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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/574,334	03/07/2007	Rudi Mueller-Walz	28069-624 NATL	5874

30623 7590 09/01/2009

MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO, P.C
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
KENNEDY, NICOLETTA	

ART UNIT	PAPER NUMBER
1611	

MAIL DATE	DELIVERY MODE
09/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,334	MUELLER-WALZ, RUDI	
	Examiner	Art Unit	
	Nicoletta Kennedy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/25/08 and 3/31/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-33 are currently pending.

Priority

This application, filed March 31, 2006, is a national stage entry of PCT/IB04/03481 filed October 8, 2004, and claims foreign priority to United Kingdom application 0323684.1, filed on October 9, 2003. Applicants have provided a certified copy of the United Kingdom application.

Claim Objections

1. Claim 7 is objected to because of the following informalities: Applicant claims "fluticasone **di**propionate" but then in claim 8, which depends from claim 7, claims "fluticasone propionate". For purposes of examination, the examiner presumes that Applicant intended "fluticasone propionate." Appropriate correction is required.

Information Disclosure Statement

2. The information disclosure statement filed August 25, 2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. Claims 1-2, 7-10, 13-16, 21, 23-25, 27-28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clarke et al. (US 2002/0103260) read in view of Trofast et al. (WO 92/18110) and Trofast (WO 01/89491).

Regarding claims 1 and 28, Clarke et al. teach an aerosol composition for a metered dose inhaler comprising formoterol fumarate dihydrate, ethanol, and HFA 134a (para. 0024). However, Clarke et al. fail to teach the water content of formoterol fumarate di-hydrate. Trofast et al. cure this deficiency.

Trofast et al. teach a process for providing water-soluble micronized substances wherein the residual water from the micronized substance is reduced by drying at an elevated temperature and/or in a vacuum (abstract). Trofast et al. explain that the invention relates to a process for providing water-soluble micronized substances which can be stored and used while maintaining the aerodynamic properties required for inhalation of such substances (p. 3, lines 5-14). The process may specifically be used on anti-asthmatic substances (claim 9).

Trofast teaches that formoterol fumarate dihydrate, when combined with a reactive species such as an aldehyde, is prone to degradation (p. 2 line 25 –p. 3, line 2). Trofast explains that when formoterol fumarate dihydrate is combined with lactose monohydrate, they form degradation products (p. 3, lines 11-16). Additionally, relative humidity influences the stability of the powder (p. 3, lines 19-20).

Although neither Clarke et al., Trofast et al., or Trofast teach the specific water content of formoterol fumarate di-hydrate, MPEP 2144.05 states that " where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation" quoting *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). The combination of Clarke et al., Trofast et al. and Trofast et al. B teach that the stability of formoterol fumarate may be improved by drying the powder prior to mixing it with the other ingredients of an anti-asthmatic aerosol composition. Thus, although the water content is not disclosed, it is not inventive to discover a workable range for the water content discernable by routine experimentation.

Regarding claims 2, 7 and 8, Clarke et al. teach that the aerosol composition for a metered dose inhaler is comprised of formoterol fumarate dihydrate, fluticasone propionate , a steroid (para. 0024).

Regarding claim 9, Clarke et al. teach that the fluticasone propionate is present at 0.250% by weight of the composition (para. 0024).

Regarding claim 10, Clarke et al. teach that the formoterol fumarate dihydrate is present at 0.012% by weight of the composition (para. 0024).

Regarding claims 13-15, and 32, Clarke et al. teach that the aerosol composition comprises HFA 134a and HFA 227, both hydrofluoroalkanes (para. 0024).

Regarding claim 16, the propellants (HFA 134a and HFA 227) are present at 97.238% by weight of the composition (para. 0024).

Regarding claim 21, Clarke et al. teach that the inhalation device may be an aerosol vial (para. 0015).

Regarding claim 23, Clarke et al. teach that the metered dose inhaler may deliver 6 to 24 micrograms of formoterol fumarate dihydrate (para. 0017). MPEP 2144.05 states that "[i]n the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists" quoting *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). In the instant case, the claimed range overlaps the range taught by Clarke et al. and is therefore prima facie obvious.

Regarding claims 24 and 25, Clarke et al. teach that the metered dose inhaler may deliver from 25 to 500 micrograms of fluticasone propionate dihydrate (para. 0017). MPEP 2144.05 states that "[i]n the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists" quoting *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). In the instant case, the claimed range overlaps the range taught by Clarke et al. and is therefore prima facie obvious.

Regarding claim 27, Clarke et al. teach that the aerosol vial may be a metered dose inhaler (para. 0015).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to have combined the teachings of Clarke et al. with those of

Trofast et al. and Trofast. One of ordinary skill would have been motivated to do so because Trofast teaches that formoterol fumarate dihydrate is unstable when combined with a reactive species such as lactose monohydrate, Trofast et al. teach a method of drying anti-asthmatic substances to stabilize them for longer shelf life, and Clarke et al. teach combining formoterol fumarate dihydrate with lactose monohydrate for use as an anti-asthmatic medication.

6. Claims 3-6, 17, 21-22, 26 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clarke et al. (US 2002/0103260) read in view of Trofast et al. (WO 92/18110) and Trofast (WO 01/89491) as applied to claims 1-2, 7-10, 13-16, 21, 23-25, 27-28 and 32 above, and further in view of Kordikowski et al. (US 2003/0223939).

The combination of Clarke et al., Trofast et al. and Trofast teaches each limitation of claim 1, from which claim 2 depends, and each limitation of claim 2, from which claims 4 and 6 depend. However, these references fail to teach the fine particle fraction of the delivered dose of formoterol fumarate dihydrate or steroid. Kordikowski et al. cure this deficiency.

Regarding claims 3 and 5, Kordikowski et al. teach particulate suspensions comprising active substances in particulate form suspended in hydrofluoroalkane propellants for use in metered dose inhalers (abstract). Kordikowski et al. specifically teach that fluticasone propionate in HFA 134a (Figure 5) and formoterol fumarate dihydrate (para. 0096) have a fine particle fraction of 35% (para. 0020). These suspensions are stored at 75% relative humidity and at 40°C (para. 0095) for varying periods of time, include 6 months (para. 0080). The fluid suspensions allow the aerosol

formulations used in metered dose inhalers to give a more uniform dosing rate throughout the useable life of the inhaler (para. 0081). The relative standard deviation in the quanitity of active substance delivered in each dose is no more than 15% (para. 0084). MPEP 2144.05 states that "[i]n the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists" quoting *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). This "no more than 15%" parameter disclosed by Kordikowski et al. fits within the variance of +/- 25% and the claimed range is therefore prima facie obvious.

Regarding claims 4 and 6, Kordikowski et al. teach particulate suspensions comprising active substances in particulate form suspended in hydrofluoroalkane propellants for use in metered dose inhalers (abstract). Kordikowski et al. specifically teach that fluticasone propionate in HFA 134a (Figure 5) and formoterol fumarate dihydrate (para. 0096) have a fine particle fraction of 35% (para. 0020). This fine particle fraction is delivered through a metered dose inhaler (para. 0021).

Regarding claim 17, Kordikowski et al. teach that ethanol is present at less than 0.01% based on the weight of the fluid vehicle (para. 0131).

Regarding claims 21-22 and 33, Kordikowski et al. teach that the aluminum metered dose inhaler need not be coated (paras. 0139-0141).

Regarding claim 26, Kordikowski et al. teach that the relative standard deviation in the quantity of active substance delivered in each dose is preferably no more than 15% (para. 0084). Although Kordikowski et al. does not specifically state that this active

substance doseage is stated on the label, it is well known in the art that inhaler labels specify the quantity of active substance delivered in each dose.

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to have combined the teachings of Clarke et al., Trofast et al. and Trofast with those of Kordikowski et al. One of ordinary skill would have been motivated to do so because the Kordikowski et al. teach the desired fine particle fraction for an inhaler and the maximum standard deviation between the intended and actual active substance dosage. Additionally, Kordikowski et al. teach a method of improving flocculation behavior such that less ethanol than usual is required as a co-solvent and such that the aluminum metered dose inhaler need not be coated, simplifying the manufacturing process for an aerosol metered dose inhaler composition.

7. Claims 11-12, 18-19 and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clarke et al. (US 2002/0103260) read in view of Trofast et al. (WO 92/18110) and Trofast (WO 01/89491) as applied to claims 1-2, 7-10, 13-16, 21, 23-25, 27-28 and 32 above, and further in view of Keller et al. (US 6,475,467).

The combination of Clarke et al., Trofast et al. and Trofast teaches each limitation of claims 1 or 2, from which claims 11-12 and 18-19 depend, and each limitation of claim 13, from which claims 29 and 31 depend. However, these references fail to teach that salts of cromoglycic acid and or nedocromil may be used in the formoterol fumarate dihydrate composition. Additionally, these references fail to teach that fluorochlorocarbons such as F218 may be used as the propellant. Keller et al. cure these deficiencies.

Regarding claim 11, Keller et al. teach the use of pharmaceutically acceptable salts of cromoglycic acid or nedocromil as carriers in an aerosol suspension formulation (abstract). The active compound in the formulation may be formoterol (column 5, line23).

Regarding claim 12, Keller et al. teach that the cromoglycic acid salts or nedocromil salts are present at not over approximately 0.7%, preferably present at 0.007 to 0.36%, and particularly present at 0.015 to 0.15% by weight of the total formulation (column 6, lines 50-56). MPEP 2144.05 states that "[i]n the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists" quoting *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). In the instant case, the claimed range overlaps the ranges disclosed by the prior art and is therefore prima facie obvious.

Regarding claim 18, Keller et al. teach that the aerosol formulations may contain surface-active agents such as oleic acid, lecithin, sorbitan trioleate, cetylpyridinium chloride, benzalkonium chloride, polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20) sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate, polyoxypropylene/polyoxyethylene block copolymers, polyoxypropylene/polyoxyethylene/ethylenediamine block copolymers, ethoxylated castor oil and the like (column 9, lines 17-25).

Regarding claim 19, Keller et al. teach that the proportion of surface-active agents, if present, can preferably be approximately 0.0001 to 1% by weight of the formulation (column 9, lines 25-27).

Regarding claims 29-31, Keller et al. teach that suitable non-toxic liquid propellants for aerosol formulations include trichloro-monofluoromethane (F11), dichlorodifluoromethane (F12), monochlorotrifluoromethane (F13), dichloro-monofluoromethane (F21), monochlorodifluoromethane (F22), monochloromonofluoromethane (F31), 1,1,2-trichloro-1,2,2-trifluoroethane (F113), 1,2-dichloro-1,1,2,2-tetrafluoroethane (F114), 1-chloro-1,1,2,2,2-pentafluoroethane (F115), 2,2-dichloro-1,1,1-trifluoroethane (F123), 1,2-dichloro-1,1,2-trifluoroethane (F123a), 2-chloro-1,1,1,2-tetrafluoroethane (F124), 2-chloro-1,1,2,2-tetrafluoroethane (F124a), 1,2-dichloro-1,1-difluoroethane (F132b), 1-chloro-1,2,2-trifluoroethane (F133), 2-chloro-1,1,1-trifluoroethane (F133a), 1,1-dichloro-1-fluoroethane (F141b) and 1-chloro-1,1-difluoroethane (F142b), alkanes such as *propane* (with regard to instant claim 30), butane and isobutane, fluorinated alkanes such as *octafluoropropane (F218)* (with regard to instant claim 31)(column 7, lines 7-25).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to have combined the teachings of Clarke et al., Trofast et al. and Trofast with those of Keller et al. One of ordinary skill would have been motivated to do so with regard to claims 11-12 because Keller et al. teach that disodium cromoglycate and nedocromil sodium are used in known metered-dose aerosols in a therapeutically or phophylatically efficacious amount. One of ordinary skill would have been motivated to combine the teachings of Keller et al. with those of Clarke et al., Trofast et al. and Trofast with regard to claims 18-19 because Keller et al. teach that the aerosol formulations may comprise a surfactant to lower the surfacxe tension of the

formulation. One of ordinary skill would have been motivated to combine the teachings of Keller et al. with those of Clarke et al., Trofast et al. and Trofast with regard to claims 29-31 because Keller et al. teach the simple substitution of known propellants.

8. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Davies et al. (US 2005/0152846) read in view of Clarke et al. (US 2002/0103260).

Davies et al. teach an inhalable pharmaceutical formulation comprising formoterol or one of its pharmaceutically acceptable salts such as fumarate (abstract, para. 30). Davies et al. additionally teach that the formulation comprises a liquefied HFa propellant and ethanol as a co-solvent (paras. 0057 and 0059). Additionally Davies et al. teach that the stability of the formulation is improved by having lower than 500 ppm of water based on the total weight of the formulation (paras. 0073 and 0112). MPEP 2144.05 states that "[i]n the case where the claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a *prima facie* case of obviousness exists" quoting *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). In the instant case, the claimed range overlaps the range disclosed by Davies et al. and is thus prima facie obvious.

However, Davies et al. do not teach that the formoterol fumarate is formoterol fumarate dihydrate. Clarke et al. cure this deficiency.

Clarke et al. teach an aerosol composition for a metered dose inhaler comprising formoterol fumarate dihydrate, ethanol, and HFA 134a (para. 0024).

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the invention to have combined the teachings of Davies et al. with those of Clarke et al. One of ordinary skill would have been motivated to do so with regard to

Clarke et al. teach a specific aerosol composition comprising formoterol fumarate dihydrate, a formoterol salt generally disclosed by Davies et al.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nicoletta Kennedy whose telephone number is (571)270-1343. The examiner can normally be reached on Monday through Thursday 8:15 to 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicoletta Kennedy/
Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/
Supervisory Patent Examiner, Art Unit 1611